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(71) Applicants: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK–2880 Bagsværd (DK). DR. REDDY'S RESEARCH FOUNDATION [IN/IN]; 7–1–27, Ameerpet, Hyderabad 500 016, Andhra Pradesh (IN).

(72) Inventors: WEIBEL, Helle; Tietgensvej 19, DK–3400 Hillerød (DK). HJORTH, Thyge, Borup; Solbakken 5, DK–3520 Farum (DK).

(74) Common Representative: NOVO NORDISK A/S; Health Care Patents, Novo Allé, DK–2880 Bagsværd (DK).

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(57) Abstract

The present invention provides a new stable pharmaceutical composition containing 5–[[4–[ 3–Methyl–4– oxo–3,4– dihydro–2–quinazolinyl] methoxy]phenyl –methyl] thiadiazolidine –2,4–dione as active ingredient.

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**New pharmaceutical composition and the process for its preparation**

The subject-matter of the present invention is a new pharmaceutical composition containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione as active ingredient and the process for its preparation.

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione and pharmaceutically acceptable salts thereof has been found useful in the treatment of type 2 diabetes acting as a insulin sensitizer as disclosed in PCT Publication WO 97/41097.

The active ingredient is present as the base or as a pharmaceutically acceptable salt, preferably as the potassium salt.

Various solutions have been proposed for the preparation of medications based on 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione.

The aim of the present invention is to provide a new composition intended for the preparation of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione with improved stability, in particular solid dosage forms thereof.

It has been found in fact that 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quina-zolinyl]meth-oxy]-phenyl-methyl]thiadiazolidine-2,4-dione and its pharmaceutically acceptable salts may decompose in the presence of and in contact with water. Further it has been observed that decomposing may occur in the presence of oxygen.

Thus, from a first aspect, the subject-matter of the present invention is a pharmaceutical composition intended for the preparation of dosage forms and in particular solid dosage forms containing an efficacious quantity of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or of one of its pharmaceutically acceptable salts as active ingredient.

The present invention is based on the surprising discovery of the fact that the stability of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts, can be considerably improved in preparations containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or of its pharmaceutically acceptable salts and antioxidant agent if the product is composed of excipients which do not contain water.

Pharmaceutically acceptable salts forming part of this invention include salts such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminium salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, together with a conventional adjuvant, antioxidant carrier, or diluent, and if desired a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or oral powders to be diluted immediately before use filled with the same, all for oral use, in the form of suppositories for rectal administration; or as pessaries for vaginal use; or in the form of sterile injectable powders for parenteral, transdermal, nasal, pulmonary and ocular use.

Within the framework of the present description and of the claims, by powders is meant any mixture of components, granulated or not, intended to be placed in solution and/or in suspension in water, or again to be ingested directly or by any other appropriate means as for example in a mixture with a food product.

In accordance with a particular characteristic of the invention, the manufacture of tablets are carried out as a direct compression.

In accordance with another particular characteristic, this composition also contains pharmaceutically acceptable excipients.

In accordance with a particular characteristic of the invention, the antioxidant agent cited above is selected from among α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT).

In accordance with a currently preferred embodiment, the antioxidant agent will be α-tocopherol.

In accordance with another particular characteristic of the invention, the diluent is lactose and/or cellulose microcrystalline, magnesium stearate, talc.

However, any other pharmaceutically acceptable diluents could be used if the diluents has a low water content.

The quantities of diluents can be easily determined by a person skilled in the art and depend of course on the final pharmaceutical form required.

Generally speaking, a composition which complies with the present invention and which are intended for the preparation of tablets, may contain, expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts:

between 100 and 400,000 parts by weight of anhydrous lactose;
between 1 and 100 parts by weight of an antioxidant;
between 50 and 500 parts by weight of pregelatinized starch;
between 1000 and 10,000 parts by weight of microcrystalline cellulose;
between 10 and 500 parts by weight of crospovidone;
between 10 and 500 parts by weight of silicon dioxide;
between 10 and 500 parts by weight of hydrogenated vegetable oil;
between 10 and 500 parts by weight of magnesium stearate;
between 10 and 500 parts by weight of hydroxypropyl methylcellulose;
between 10 and 500 parts by weight of hydroxypropyl cellulose;
between 1000 and 10,000 parts by weight of Mannitol;

between 10 and 500 parts by weight of stearic acid;
between 10 and 500 parts by weight of Titanium Dioxide;

According to a preferred embodiment of the invention the water content of the excipients is very low. More specifically the water content in the diluents is very low in order to minimize the water content of the pharmaceutical composition. Lactose is used in its anhydrous form.

Furthermore, all excipients may be applied in a dry form.

In accordance with a second aspect, the subject-matter of the present invention is a pharmaceutical preparation, in the form of tablet or powder, characterised in that it contains a composition as defined previously associated if required with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

The choice of these additives and their quantity can easily be determined by a person skilled in the art.

Another manufacturing process for pharmaceutical compositions according to the invention is mixing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, one or more antioxidants and other pharmaceutical excipients followed by melt granulation in a high shear mixer. Hydrogenated, vegetable oil, waxes or other low temperature melting binders can be used. The granules can be filled into capsules, compressed into tablets or used in other pharmaceutical dosage forms.

More preferably the manufacturing process applied is direct compression of tablets, wherein 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, one or more antioxidants and other excipients suitable for direct compression are mixed followed by tabletting.

Yet, another preferred embodiment of the manufacturing process is wet granulation, where granules are obtained by wet massing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, together with one or more antioxidants and other excipients.
It is assumed that the contact time with water have to be very short.

The most preferred process comprises the direct compression whereby 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione is kept at conditions of low water vapour pressure.

A sweetener may be a natural sugar such as sorbitol or a synthetic product such as saccharine or aspartame.

When the antioxidant selected is ascorbylpalmitat, propylgallat, which is a powder, it can be advantageous to mix it in an appropriate excipient such as α-tocopherol succinat, lactose or cellulose micrycrystalline.

The present invention will further be illustrated with the following non-exhaustive examples.

In Example 1 through 4 the tablets were prepared according to the following procedure:

The active ingredient is mixed with cellulose microcrystalline in a drum mixer for 10 minutes. Lactose is added and the mixing continued for further two minutes.
The lubricants are added and the mixing continued for further two minutes.

## EXAMPLE 1

25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 807227

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt, 003/97 | 9% |
| Cellulose Microcrystallline | 20% |
| Lactose | 66% |
| Magnesium Stearate | 0.5% |
| Talc | 4.5% |

## EXAMPLE 2

50 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt tablets 807237

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt, 003/97 | 18% |
| Cellulose Microcrystalline | 20% |
| Mannitol | 57% |
| Magnesium Stearate | 0.5% |
| Talc | 4.5% |

EXAMPLE 3

50 mg 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 731725

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 18% |
| Lactose | 81.5% |
| Magnesium stearate | 0.5% |

EXAMPLE 4

0.25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 728625

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09% |
| Mannitol | 98% |
| Magnesium stearate | 2% |

EXAMPLE 5

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09% |
| Hydrogenated vegetable oil | 6.25% |
| Talc | 5% |

| | |
|---|---|
| α-tocopherol | 50% of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt |
| Lactose DCL21/Mannitol | Up to 200 g |

The granulate is manufactured in a Baker Perkins 1 L high-shear mixer - using a water bath of 70°C. The mixing is carried out at 3000 RPM, chopper 6000 RPM and the granulation is performed at approx. 70°C. The hot granulate is sieved through sieve 1.25 μm, and the cold granulate through sieve 1000 μm. The glidant is added with a card for 2 min. The tablets are manufactured using a Diaf tablet machine with 9 mm punch.

In order to protect against light and improve the appearance of the tablets, the tablets are film-coated.

The tablets were coated with the following film-coating composition where an amount of coating material of 5 mg/cm$^2$ were chosen as being satisfactory with respect to stability of the tablets:

| | |
|---|---|
| Methylhydroxypropylcellulose, Ph. Eur..... | ~ 4.34 mg/tablet |
| Titanium Dioxide, Ph. Eur..... | ~ 1.73 - |
| Purified Water, Ph. Eur..... | q.s. - |

Talc, Ph. Eur. (Added as polishing agent at the end of the film-coating process (0.5 % w/w of tablet core). Absorbed amount is not quantified.

## EXAMPLE 6

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09% |
| Povidone | 7.5% |
| Hydroxypropylmethyl cellulose | 1.5% |
| Croscarmelose sodium | 1.56% |
| Talc | 1.1% |
| Magnesium stearate | 0.5% |
| Lactose 300 mesh | up to 200 g |

The granulate is manufactured by Baker Perkins 1 L intensive mixer. Dry mixing were carried out at 500 RPM, chopper 1500 RPM and granulation 1000 RPM and 2000 RPM. The wet

granulate is sieved through sieve 1.25 μm and the dry granulate through sieve 1000 μm. The glidant is admixed with a card for 2 min. The tablets are manufactured by Diaf tablet machine with 9 mm punch.

## EXAMPLE 7

Composition: Oral Powder, 1 mg/ml, 100 ml

| | |
|---|---|
| 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione potassium salt | 0.1096 g |
| Mannitol | 2.5 g |
| Hydroxypropyl-β-cyclodextrin | 10 g |

To be diluted with 92 mL water before use.

## EXAMPLE 8

Composition: Oral Powder, 10 mg/ml, 100 ml

| | |
|---|---|
| 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione potassium salt | 1.096 g |
| Mannitol | 2.5 g |
| Hydroxypropyl-β-cyclodextrin | 10 g |
| Sodium Carbonate, anhydrous, $Na_2CO_3$ | 15 mg |

To be diluted with 92 mL water before use.

CLAIMS

1. Pharmaceutical composition comprising
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and optionally a pharmaceutically acceptable carrier.

2. A composition according to claim 1 in the form of a tablet, a powder or a capsule.

3. A process for the preparation of a composition according to claim 1 or 2 which comprises the step of forming a mixture of:
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and one or more pharmaceutically acceptable carriers.

4. A process for the preparation of a composition according to claim 1 or 2 which comprises the following steps:
forming a mixture according to claim 3,
and direct compression of the mixture with excipients of a low water content.

5. A process according to claim 3 or 4 characterized in that the steps are carried out at low water vapour pressure and low oxygen pressure.

6. A pharmaceutical composition comprising
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and pharmaceutically acceptable excipients with low water content and an antioxidant.

7. The pharmaceutical composition according to claim 6 in the form of a tablet, a powder or a capsule.

8. The pharmaceutical composition according to claim 6 or 7 containing, expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts and be-

tween 1 and 100 parts by weight of an antioxidant and the pharmaceutically acceptable excipients selected among the following:
between 100 and 400,000 parts by weight of anhydrous lactose,
between 1 and 100 parts by weight of an antioxidant,
between 50 and 500 parts by weight of pregelatinized starch,
between 1000 and 10,000 parts by weight of microcrystalline cellulose,
between 10 and 500 parts by weight of crospovidone,
between 10 and 500 parts by weight of silicon dioxide,
between 10 and 500 parts by weight of hydrogenated vegetable oil,
between 10 and 500 parts by weight of magnesium stearate,
between 10 and 500 parts by weight of hydroxypropyl methylcellulose,
between 10 and 500 parts by weight of hydroxypropyl cellulose,
between 1000 and 10,000 parts by weight of Mannitol,
between 10 and 500 parts by weight of stearic acid,
between 10 and 500 parts by weight of Titanium Dioxide.

9. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are selected among from the following:
between 100 and 400,000 parts by weight of anhydrous lactose,
between 50 and 500 parts by weight of pregelatinized starch,
between 1000 and 10,000 parts by weight of microcrystalline cellulose,
between 10 and 500 parts by weight of crospovidone,
between 10 and 500 parts by weight of silicon dioxide,
between 10 and 500 parts by weight of hydrogenated vegetable oil,
between 10 and 500 parts by weight of magnesium stearate,
between 10 and 500 parts by weight of hydroxypropyl methylcellulose,
between 10 and 500 parts by weight of hydroxypropyl cellulose,
between 1000 and 10,000 parts by weight of Mannitol,
between 10 and 500 parts by weight of stearic acid,
between 10 and 500 parts by weight of Titanium Dioxide,
expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts.

10. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are selected from the following:
lactose and/or cellulose microcrystalline, magnesium stearate or talc.

11. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients have a low water content.

12. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients have a very low water content.

13. The pharmaceutical composition according to claim 6 or 7 wherein the pharmaceutically acceptable excipients are in a dry form.

14. The pharmaceutical composition according to claim 6 or 7 wherein the antioxidant is selected from the following:
α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) or butylated hydroxy toluene (BHT).

15. The pharmaceutical composition according to claim 6 or 7 wherein the antioxidant is α-tocopherol.

16. The pharmaceutical composition according to claim 1,2, 6 or 7 associated with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

17. A process for the preparation of a composition according to claim 6 or 7 which comprises the step of forming a mixture of:
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and one or more pharmaceutically acceptable excipients and an antioxidant.

18. A process for the preparation of a composition according to claim 6 or 7 which comprises the following steps:
forming a mixture according to claim 17, and direct compression of the mixture.

19. A process according to claim 17 or 18 characterized in that the steps are carried out at low water vapour pressure and low oxygen pressure.

20. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 9% |
| Cellulose Microcrystallline | 20% |
| Lactose | 66% |
| Magnesium Stearate | 0.5% |
| Talc | 4.5% |

21. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 18% |
| Cellulose Microcrystalline | 20% |
| Mannitol | 57% |
| Magnesium Stearate | 0.5% |
| Talc | 4.5% |

22. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 18% |
| Lactose | 81.5% |
| Magnesium stearate | 0.5% |

23. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09% |
| Mannitol | 98% |
| Magnesium stearate | 2% |

24. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09% |
| Hydrogenated vegetable oil | 6.25% |
| Talc | 5% |
| α-tocopherol | 50% of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt |
| Lactose DCL21/Mannitol | Up to 200 g. |

25. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09% |
| Povidone | 7.5% |
| Hydroxypropylmethyl cellulose | 1.5% |
| Croscarmelose sodium | 1.56% |
| Talc | 1.1% |
| Magnesium stearate | 0.5% |
| Lactose 300 mesh | up to 200 g. |

26. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.1096 g |
| Mannitol | 2.5 g |
| Hydroxypropyl-β-cyclodextrin | 10 g |

and diluted with 92 mL water before use.

27. The pharmaceutical composition according to anyone of the preceding claims comprising the following:

| | |
|---|---|
| 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 1.096 g |
| Mannitol | 2.5 g |

| | |
|---|---|
| Hydroxypropyl-β-cyclodextrin | 10 g |
| Sodium Carbonate, anhydrous, $Na_2CO_3$ | 15 mg |

and diluted with 92 mL water before use.

5

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00663

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/427, A61K 31/517, A61P 5/50 // C07D 417/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 9741097 A2 (DR. REDDY'S RESEARCH FOUNDATION), 6 November 1997 (06.11.97), claims 17,18,23,24; page 34 - page 36 | 1-27 |
| X | WO 9618386 A1 (ENBALT TRADING LIMITED), 20 June 1996 (20.06.96) | 1-27 |
| A | WO 9506461 A1 (SMITHKLINE BEECHAM CORPORATION), 9 March 1995 (09.03.95), page 17, line 1 - line 30; the claims | 1-27 |

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 February 2000 | 13 -04- 2000 |
| Name and mailing address of the ISA:<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Gerd Strandell/EÖ<br>Telephone No. +46 8 782 25 00 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00663

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 9217161 A1 (THE PROCTER & GAMBLE COMPANY), 15 October 1992 (15.10.92), page 2; line 20 - line 32; the claims<br>-- | 1-27 |
| P,A | EP 0945134 A1 (BOEHRINGER INGELHEIM PHARMA KG), 29 Sept 1999 (29.09.99), page 10, line 39 - page 12, line 37<br>--<br>-------- | 1-27 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00663

**Box I** **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The terminology "thiadiazolidine-2, 4-dione" is confusing. It is clear, confer the reference in the description page 1, line 8-line 11 to WO 97/41097, that "thiazolidine-2, 4-dione" is intended and the search is carried out accordingly.

**Box II** **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00663

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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